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Early behaviour and development in breast-fed premature infants are influenced by omega-6 and omega-3 fatty acid status

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ABSTRACT

Background: The requirement of essential fatty acids (EFA) for the development of the brain is well documented.
Objective: To investigate the early neurological development at term and 44 weeks gestational age in preterm infants in relation to EFA concentrations in breast milk and in infants' and mothers' plasma phospholipids.
Method: Fifty-one premature infants and their mothers were consecutively included in the study. The median gestational age was 34 weeks (range 24–36). The motor quality, motor and behavioural development were assessed by General Movements (GMs), the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) and a Self Regulation Scale.
Results: Mother's education and gestational age correlated to several outcome variables. Multiple regression with correction for background factors showed negative associations between early breast milk concentrations of Mead acid and GMs and between AA and the BNBAS clusters Orientation and Range of States, respectively. Between 40 and 44 weeks gestational age, no expected increased scores were observed for Regulation of States, Range of States and Self Regulation. During the corresponding time, increased concentration of linoleic acid in mothers' plasma was negatively associated with improvement in Orientation and increased concentration of EPA in the infants' plasma was positively associated with improvement in Autonomic Stability.
Conclusions: The major omega-6 fatty acids and Mead acid were negatively associated with early development and omega-3 fatty acids positively associated. Mother's education and the gestational age influenced the outcome more strongly than mother's and infant's morbidities. Further follow-up will elucidate the significance of these early findings.

1. Introduction

Major advances in perinatal and neonatal care have reduced mortality, but still many infants born preterm suffer from minor to severe disabilities including motor impairments, learning disabilities, Attention-Deficit Hyperactivity Disorder (ADHD), speech and language delay, attachment disturbances, behavioural problems and general cognitive disabilities [1–7]. More boys than girls seem to have these problems [5]. Late preterm infants [8] born at 34–36 weeks of gestational age, with apparently uncomplicated perinatal periods, have shown more clinical problems than full term infants [9], including minor neurodevelopmental abnormalities and school problems [10]. It has also been suggested that the prevalence of ADHD is increasing among these infants [7]. A need to understand better the different factors, which have an impact on the development of premature infants, has focused attention on nutritional factors.

Perinatal nutrition is important for growth and neurodevelopment [11,12], and most of the long chain polyunsaturated fatty acids (LCPUFA) are transmitted from the mother to the foetus during the third trimester and are accumulated in the central nervous system and other organs, especially the liver [13]. The infant is thus dependent on the mother's EFA status. When born prematurely, the umbilical transfer of LCPUFA is interrupted and low intake of breast milk or an insufficient supply of LCPUFA in the breast milk might pose a risk for the future development of the preterm infant. Most studies have focused on comparisons between breast milk and formula supplemented feedings and little attention has been given to the fact that the FA concentration in breast milk varies, reflecting the mother's dietary intake and stores. Breast milk may thus contain low levels of LCPUFA and not be as ideal as expected [14].

The requirement of essential fatty acids (EFA) for the development of the brain is well documented [15–17]. Several studies have demonstrated a positive effect of neonatal supplementation of LCPUFA both

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on neurodevelopment and motor function and quality in full term infants [18–20]. There have been conflicting results concerning supplementation of formulas by LCPUFA for preterm infants. Beneficial effects on neurodevelopment up to 4 months of age have been reported in term infants [21]. Increase in visual acuity was seen in preterm infants at 2 and 4 months given EFA/LCPUFA compared to a control group [20]. No conclusive evidence of long-term neurological benefits was obtained in large Cochrane reviews of randomized controlled trials including both preterm [22,23] and term infants [24].

This study is part of a long-term project following nutrition, growth and development in a cohort of premature infants up to 5 years of age. We have previously reported that 75% of the mothers of these preterm infants had an energy intake below recommendations and that 60% had a low intake of EFAs, especially of the omega-3 series [25]. Mead acid (20:3$n-9$, eicosatrienoic acid), often used as ratio to arachidonic acid (20:4$n-6$, AA), and considered an indicator of EFA deficiency [26], showed high concentration in the mothers' and infants' plasma phospholipids and in breast milk at one week postnatal age. The wide variations of PUFA and LCPUFA in the studied group raised the question as to whether these findings would be linked to the early neurological and motor development of the infants. Our hypothesis was that an influence on development would be possible to detect at a very early age.

The aim of the present study was to explore if the main EFA concentrations in breast milk and in mothers' and infants' plasma phospholipids during the early postnatal period were associated with the infant's very early neurological and motor development. The first objective was to investigate if assessments with BNBAS [27], GMs [28–30] and a Self Regulation Scale [31] at the ages corresponding to 40 and 44 weeks of gestation were associated with the major omega-6 and omega-3 FA concentrations in early breast milk and in mothers' and infants' plasma phospholipids at those ages. Our second objective was to determine whether possible changes in the concentrations of these fatty acids in mothers' and infants' plasma over time were associated with the infants' individual development during the corresponding time.

2. Methods

The study was approved by the Ethical Committee of the Sahlgrenska Academy of the University of Gothenburg and was performed at a local community hospital with well-established neonatal care. After informed consent from the mothers, 51 newborn infants, 23 boys and 28 girls, born after a median age of 34 (24–36) gestational weeks were consecutively included. The care in the ward was family-centered with individualized developmental care for the infants. There were eleven pairs of twins. Basic data of the premature infants are presented in Tables 1a and 1b [32]. The dietary intake of the mothers, and the FA analyses of breast milk and phospholipids in plasma samples from mothers and infants, have previously been described in detail [25].

Table 1a
Basic data of 51 preterm infants, median (range). Mean standard deviations (SD), for gestational age with range in brackets.

	Body measurements		SD for gestational age	
Gestational age (weeks) at birth	34	(24–36)		
Weight (g)	2070	(740–3170)	−0.77	(−5.29 to 1.42)
Length (cm)	45	(45.0–52.0)	−0.58	(−3.43 to 2.99)
Head circumference (cm)	30.9	(21.0–35.0)	−0.12	(−1.84 to 1.60)
At 40 weeks				
Weight (g)	3270	(2435–4160)	−0.96	(−3.17 to 1.01)
Length (cm)	50	(45.0–55.5)	−0.71	(−4.02 to 2.24)
Head circumference (cm)	35.3	(32.0–37.6)	−0.02	(−1.44 to 1.63)
At 44 weeks				
Weight (g)	4248	(2845–5410)	Reference values	
Length (cm)	54.2	(49.0−59.5)	Not available	
Head circumference (cm)	37.6	(36.0−40.2)		

Table 1b
Background factors of mothers and infants, number, percentage of total in brackets.

Mothers' education		
Compulsory schooling	5	(12.5%)
Secondary school	18	(45.0%)
College or university	17	(42.5%)
Mothers' morbidity		
Group		
1 (Bleeding, section)	5	(12.5%)
2 (Preeclampsia or HELLP syndrome, section)	8	(20.0%)
3 (Eclampsia, convulsions, section)	2	(5.0%)
Mother smoking	8	(20.0%)
Infants' morbidity		
Group		
1 (Suspicion, fast recovery)	11	(21.5%)
2 (Clinical signs, treated)	5	(10.0%)
3 (Clinically very ill)	4	(7.8%)
Infants small for gestational age	9	(18.0%)
Twin status	22	(43.0%)

Several maternal and infant background variables were assessed, including the mothers' education, smoking habits and morbidity, the infants' gestational age at birth, if proportionate for gestational age (small for gestational age was defined as more than 2 standard deviations below mean weight for gestational age), twin status, infants' morbidity and sex. Only mothers who smoked during pregnancy were classified as smokers. The background variables: twin status, small for gestational age, and maternal smoking, were treated as binary variables.

Infants' and mothers' morbidity were divided into 3 groups, respectively. Group 1 (11 infants) had suspected infection, and were given antibiotics because of increased CRP, but blood cultures were negative for bacteria. The infants responded to the medical therapy immediately and became well within a few days. Group 2 (5 infants) had clinical signs such as poor skin colour, bradycardia or hypoglycemia for more than 6 h and needed assisted ventilation for a few days, but soon recovered. Group 3 (4 infants), were clinically very ill and demanded immediate intensive care (1 confirmed cerebral bleeding, 2 status post severe asphyxia, 1 had repeated episodes of poor status with suspicion of general infection). Two infants had severe asphyxia at 5 min (Apgar scores 0–3) and 5 infants light asphyxia (Apgar scores 4–6) and the rest were normal. Cerebral ultrasound was performed on 15 infants, but only one had a bleeding in the thalamic area, which slowly resolved over time. Two patients had a slight disproportion in width of the lateral ventricles, but all others were normal.

In the mothers, Group 1 (5 mothers), started bleeding during labour and acute caesarian section was performed. The mothers were in good condition. In Group 2 (8 patients), the mothers had severe preeclampsia or HELLP syndrome, also requiring acute section and in Group 3 (2 mothers) had severe eclampsia with convulsions and elective section was performed before labour had started. Since the number of infants and mothers in these groups was low, we could not perform statistically meaningful analyses, and therefore had to omit these group classifications from the analyses.

3. Instruments

3.1. General Movements assessments (GMs)

The GMs were assessed at 40 week gestational age. The assessment consisted of a video recording of spontaneous motility in a supine position [29,33,34]. Only movements during an awake, active, non-crying behavioural state were assessed. The recordings lasted about 10 min. The observation of GMs activity in an adequate state lasted for at least 2 min.